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09/161,680	09/28/1998	UWE BORNSCHEUER	48429	7944

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EXAMINER
KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
1652	28

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/161,680	Applicant(s) BORNSCHEUER ET AL.
	Examiner Kathleen M Kerr	Art Unit 1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (Paper No. 26, mailed on December 10, 2002), Applicants filed an amendment and response received on April 15, 2003 (Paper No. 27). Said amendment amended Claims 12 and 22. Thus, Claims 12-23 are pending in the instant Office action and will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority for the foreign application 19743683.8 filed in Germany on October 2, 1997.

Drawings

3. As previously noted, the drawings have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter.

Withdrawn - Objections to the Specification

4. Previous objection to the specification for lacking appropriate sections entitled is withdrawn by virtue of Applicant's amendment.

5. Previous objection to the specification for being confusing on page 9 concerning Formula (II) 1 and 3 is withdrawn by virtue of Applicants' amendment.

6. Previous objection to the specification for being confusing considering the unclear abbreviations in Table I on page 10 is withdrawn by virtue of Applicants' amendment.

Maintained - Objections to the Specification

7. Previous objection to the specification for a confusing structure using parentheses is maintained in part. The structure of "_____ (=_____)", not just the particular occurrence noted on page 6, is unclear. This sentence structure appears throughout the specification, even in the amendments filed on April 15, 2003, and remains unclear as previously noted. Perhaps a structure such as ---____, for example ____--- would be appropriate. Moreover, in the amendment, a triple bar in place of the previous equals sign is found; the nature of its use is unclear. Correction is required.

Withdrawn - Objections to the Claims

8. Previous objection to Claims 12 and 22 for having an improper form is withdrawn by virtue of Applicants' amendment.

Withdrawn - Claim Rejections - 35 U.S.C. § 112

9. Previous rejection of Claims 12-23 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "substrate specificity" is withdrawn by virtue of Applicants' amendment removing said term from the claims.

Maintained - Claim Rejections - 35 U.S.C. § 112

10. Previous rejection of Claims 12-23 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "functional derivative" is maintained. Applicants argue that the insertion

of further description into the claim renders the term clear. This is not the case. Still, one of skill in the art would ask "What are metes and bounds of the function that must be retained? Some particular resistance? The mutator strain functionality?" Without clear answers from these questions, the term is unclear. The Examiner notes that the addition terms in the claim define the structure of a functional derivative but fail to define which "function" is maintained. This is the clarification that is required.

11. Previous rejection of Claim 20 under 35 U.S.C. § 112, second paragraph, as being indefinite for the abbreviations "PS" and "AH" is maintained. Applicants argue that in light of the amendment to Table I, the abbreviation are now clear. This is not the case. Nowhere in the amendment does the following structure appear ---lipase (PS)--- which structure is required to clearly define the abbreviation "PS" as a lipase. Moreover, all abbreviations must be defined upon their first appearance in the claims, regardless of their clarity in the specification. Thus, Claim 20, itself, must be amended to clarify the abbreviations used therein.

12. Previous rejection of Claims 12-23 under 35 U.S.C. § 112, first paragraph, written description, is maintained. Applicants' arguments, which are generically proposed against the instant rejection and the rejection set forth below, have been fully considered but are not deemed persuasive. Applicants argue that the specification "clearly supports this range of functional equivalents as originally claimed". However, as the Examiner previously noted, "although the genus of functional derivatives of the mutator strain *E. coli* XL1-Red is discussed in the specification, there is no evidence that any representative species of such a large and varied genus was in the possession of the inventors at the time of filing. To satisfy the written

description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed. The specification does not disclose any representative species of any of the recited classes of functional derivatives of a mutator strain, with or without identifying characteristics. Therefore, Claims 12-23, as written, fails to satisfy the written description requirement to the full extent of their scope." Without a representative number of species of the claimed genus of "functional equivalents" of the mutator strain used in the claimed methods, the full scope of the claimed invention is not adequately described.

Applicants note the application by the Examiner of "Lilly"; however, that application is not pertinent to the instant rejection. See below arguments.

13. Previous rejection of Claims 12-23 under 35 U.S.C. § 112, first paragraph, written description, is maintained. Applicants' arguments have been fully considered but are not deemed persuasive. Applicants argue that an error in the quotation of the Lilly court case renders the case inapplicable. While the Examiner agrees, in part, with this rendering, the previously presented logic based on Lilly is applicable. As previously noted,

> "The instant claims are directed to methods altering an enzyme's substrate specificity using (1) a random mutator strain, (2) a gene for the unmutated enzyme, (3) a new, desired substrate for the enzyme, and (4) a screening procedure...
>
> The instant claims are drawn to using *any* enzyme and *any* new substrate to produce a new enzyme with altered substrate specificity relative to the original. The specification provides a *single* example of such enzymes and substrates and

> no correlations between their structures and functions. The field of enzymology is enormous with six major enzyme categories (provided by the Enzyme Commission in the form of E.C. numbers) and numerous subdivisions within each category based on the functionality of each enzyme. For example, how different from the typical esterase substrate can you get and still practice the claimed method effectively? Is there any correlation between how different the substrate and how many rounds of mutagenesis are necessary to achieve the desired goal? Are there occasions that structurally the method will not work? Considering all these questions, it is clear that the written description of a single example in the instant specification does not adequately describe the genus of "reagents" claimed for use in the methods."

While Lilly is drawn to claims to genetic material, *per se*, similar materials are required for the practice and completion of the claimed methods. A method is unable to be practiced without a complete description of the reagents used in that method. Since the invention is claimed in such broad and inexact terms, written description for the genera noted is required so that one of skill in the art would recognize Applicants were in possession of the claimed invention. That is not the case here as noted previously (see above) considering all the lack of description for the field of enzymology. The instant rejection is maintained.

14. Previous rejection of Claims 12-23 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for specific examples of the methods proven to achieve their goals, does not reasonably provide enablement for methods using all enzymes, all substrates, and all possible mutator strains is maintained. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants arguments center around the Wands factors – factors previously addressed by the Examiner.

> "The Examples in the instant specification describe synthesizing a substrate (let's call it substrate A) that the inventors wanted to have an enzyme

> utilize to produce a particular product, wherein the product is difficult to organically synthesize; the chemical reaction is a lipase or esterase type reaction. Since no known enzyme naturally performs this reaction with substrate A, the inventors subjected an esterase gene to random mutagenesis in the hopes of altering a naturally occurring lipase or esterase to now accept substrate A and catalyze the desired reaction. These mutant esterases were screened for the desired activity. No guidance is suggested for the use of other enzymes, with other catalytic activities. No guidance is suggested for what sort of substrates can be utilized – how alike to the original substrate they must be. The amount of experimentation to randomly screen for a "novel" enzyme activity is wholly dependent on the type of substrate looking to be used by the "new" enzyme – a substrate very similar to the original is likely to take little experimentation while a substrate unlike the original is unlikely to produce any positive result at all. No guidance as to where to draw this line is offered by the specification as originally filed. The most striking of the Wands factors to be considered is the extreme unpredictability in the claimed methods. It is unclear from the art and the specification which enzymes might facilitate such methods. Some enzymes, as tested by site-directed mutagenesis, can tolerate little mutation in their active sites and/or substrate binding pockets and still perform their catalytic activities. These would not be useful for the claimed methods. Other enzymes do not have as much know about their structures, and their effectiveness in the claimed methods is wholly unpredictable. For all these reasons, the instant claims are not enabled to the full extent of their scope."

Applicants argue that the Examiner's citation of "unlikely" positive results is a matter of routine screening. However, the point precisely made by the Examiner was the lack of predictability of a positive outcome upon practicing the claimed method steps. By definition, routine screening, while possibly being arduous, **must have a predictable outcome to be**, in fact, **ROUTINE**. Applicants cite case law concerning the determination of extensive screening for the production of monoclonal antibodies. The distinct difference in that fact scenario was that the production of monoclonal antibodies is a virtue certainty after having practiced routine procedures. That is not the case here – the production of a new enzyme is in no way predictable even with enormous amounts of experimentation.

Applicants also argue that "working examples of how the present procedures are carried out...should obviate any perceived necessity for additional working examples". Firstly, the instant specification provides a single working example. Secondly, while other working examples are not required for enablement, satisfaction that undue experimentation would not be required to practice the claimed invention to the full extent of its scope is required. Other working examples are a simple way to satisfy this requirement. A show of predictability is another. Neither the art nor any discussion in the specification and/or applicant's arguments have demonstrated such predictability. For all these reasons, the instant rejection is maintained.

Withdrawn - Claim Rejections - 35 U.S.C. § 103

15. Previous rejection of Claims 12, 16, and 21 under 35 U.S.C. § 103(a) as being unpatentable over Wilks *et al.* in view of Greener *et al.* is withdrawn by virtue of the Examiner's reconsideration in light of Applicants' arguments.

NEW OBJECTIONS/REJECTIONS

Objections to the Specification

16. The specification is objected to for being confusing on page 3-4, as amended on April 15, 2003, where, as amended, it reads "The generation of a new catalytic activity reduced the K_m or increases the k_{cat} or both". This is confusing because if no activity was present prior to mutation, from what value should the K_m or k_{cat} be measured as reduced or increased? Clarification is required.

17. The amendment filed April 15, 2003 (Paper No. 27) is objected to under 35 U.S.C. § 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

> On page 10, in Table I, the insertions of "lipase", "Amano", "Lipozyme", and "Novozyme"are all new matter. Nowhere in the specification are the lipases and esterases in the table previously defined. Moreover, the previously used abbreviations of "PS" and "AH", etc. were not clearly referring to these new matter terms.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claims 12-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "relA1" is unclear. Other gene names are clear as found in the specification, but the relA1 gene remains undefined in the specification as originally filed. Clarification is required.

19. Claims 12-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear how an "impeding enzyme activity" can be determined

when what is being produced is a "new catalytic activity". How can one of skill in the art recognize what might impede when the new catalytic activity is undefined. Similarly, the choice of enzyme substrate for selection is unclear if this "new" catalytic activity is undefined. How should this substrate be decided upon? Additionally, is the new catalytic activity in addition to the defined enzyme activity at the end of the claim or is it in place of the original catalytic activity defined at the end of the claim. In other words, should a lipase also now possess dehydrogenase activity (not in the list)? Should a dehydrogenase now possess lipase activity? Can the original activity be maintained? Must it be maintained? Clarification on all these points is required.

Conclusion

20. Claims 12-23 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

KMK
June 30, 2003